REVIEW ARTICLE

Oral Transmucosal Drug Delivery: A Potential Route To Treat Migraine

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Received: 29th Sep, 2024; Revised: 12th Nov, 2024; Accepted: 25th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT
Migraine is a complex neurological disease. Migraine headaches described as vascular headaches cause a throbbing and pulsating pain around the head. A migraine attack involves stimulating the sympathetic nerve system, and increased sympathetic activity leads to nausea, vomiting, and diarrhea. Therefore, treatment of migraine requires immediate onset of action of the drug to give fast relief from the pain. Absorption of drugs directly through the oral cavity is one of the efficient ways of treating various diseases. The oral cavity has low enzymatic activity, ease of access for patients to receive and administer medication, and high vascularization and permeability allowing pharmacological compounds to reach the bloodstream immediately. Oral Transmucosal formulations such as mouth-dissolving strips, buccal tablets, buccal patches, and bioadhesive films, sublingual formulations, soft palatable films provide better bioavailability and tackle the main drawbacks of oral therapy, including hepatic biotransformation, varying drug absorption across the gastrointestinal system, and enzymatic degradation. The effects of these formulations might be both systemic and localized. In this paper, a comprehensive review has been made to discuss the causes, types, and treatment of migraine. The role of Oral Transmucosal formulations in the prepared for the treatment of migraine.

Keywords: Bioavailability, Bioadhesive films, Buccal route, Migraine, Nanocarriers, Oral cavity
How to cite this article: Morris S, Badola A, Nainwal N, Ghalwan D, Soni P. Oral Transmucosal Drug Delivery: A Potential Route To Treat Migraine. International Journal of Drug Delivery Technology. 2024;14(4):2511-21. doi: 10.25258/ijddt.14.4.73
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

The oral cavity comprises the mouth's upper lips, lower lips tongue, cheeks (buccal cavity), hard palate, soft palate, and base (floor). The term "oral mucosa," which refers as the moist tissue or the lining of the oral cavity, encompasses the buccal, sublingual, gingival, palatal, and labial mucosa.[1] The surface area of buccal mucosa is 100 cm^2 which, delineates the inner cheek lining, the gap between the upper lip and lower lip, and the gums. Its primary purpose is to shield tissues from the entry of foreign material that causes harm and also protects from damages (mechanical and chemical).[2] From a structural standpoint, it is a multilayer lining composed of the outmost layer of outer epithelial tissue and specialized extracellular matrix i.e.basement membrane, which are secured in place by the lamina of connective tissue lamina. The oral mucosa's permeability, pH, enzyme activity, volume of saliva flow rate, and other factors all affect how well drugs are delivered through it. On the other hand, vascularization, different epithelial cell composition, and mucosal thickness all affect permeability.[3] Very minute quantity of neutral and polar lipids, such as cholesterol-sulfate and glucosyl ceramides, are present in the non-keratinized epithelial tissues of the buccal and sublingual mucosa Ceramides are only slightly present. Therefore, because it contains non-polar lipids like ceramides and acylceramides, it is more permeable than the keratinized epithelium.[4,5] The thickness of sublingual-mucosa is 100–200 μm which is comparatively thinner and has more blood vessels than the buccal mucosa whose thickness is 500–800 μm so sublingual mucosa is more permeable.[6] for a rapid onset of drug action, sublingual mucosa is preferred but on the other hand, buccal-mucosa is best suited for local and systemic drug delivery. The trans-soft palatal route has many advantages over other transmucosal routes like buccal, and sublingual,. because of nonkeratinized cells, less salivary secretion leads to minimum drug loss into the saliva.[7]

Migraine

A complicated neurological ailment called migraine is thought to be the main cause of headaches that result in disabling conditions A migraine is a recurrent headache disorder that presents as a unilateral, throbbing headache ranging from mild to severe, following the Recent International Classification of Headache Disorders. The most extensive type of vascular headache, that generates a shivering and fluctuating pain all over the head, is migraine. It includes the brain's abnormally sensitive arteries, which might set off triggers that frequently cause sudden changes in the artery's diameter or spasms. This causes more arteries in the brain and scalp to enlarge, which causes excruciating headache pain[8] Migraine is marked as a chronic condition characterized by recurrent episodes of headache, transitory focal-neurologic symptoms, or both. The pain is so severe that it weakens one's capacity to move around

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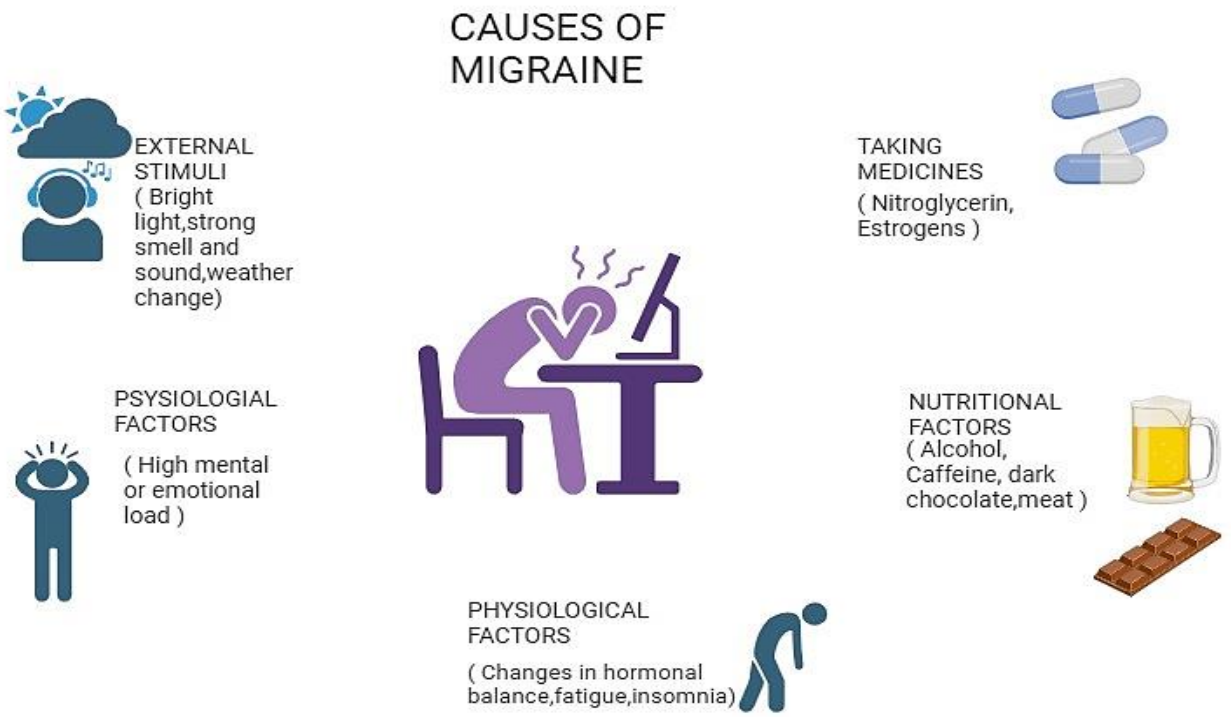

Figure 1. Causative factors of Migraine

physically, necessitating bed rest in certain cases, and it also interferes with the proper functioning of other systems of the body.[9] Frequent signs and symptoms include nausea, vomiting, and/or photophobia and phonophobia. There are two types of migraine: If the number of headache days per month is fewer than 15, it is known as EM (episodic migraine), and if it is equal to or greater than 15 for a period longer than three months, it is known as CM (chronic migraine).[10] The severity of pain in migraine impairs the ability of other bodily systems to function. They achieve this by stimulating the sympathetic nervous system, and there is strong bio-chemical evidence available that the sympathetic nervous system is activated during a migraine attack. The gastrointestinal tract is the most prominently affected system, with its distal portion accelerating and its proximal part being inhibited. The suppression of the proximal portion also hampers the absorption of oral drugs. The suppression of stomach emptying into the small intestines is what causes the delayed emptying, which results in poor absorption. For this reason, buccal formulations are used which bypass first-pass metabolism and directly and directly absorbed in the blood.[11,12] A summary of causative factors responsible for migraine is shown in Figure 1.[13]

Diagnosis and Treatment of Migraine

Prophylactic and abortive medicines are being employed as pharmacologic therapies for migraine headaches. Figure 3 depicts the severity of migraine and the treatment preferred in that case[14] Various classes of drugs used for the treatment of migraines are shown in Figure 4[15,16]. CGRP(Calcitonin gene-related peptides) inhibitors for e.g. Eranmuab are used in migraine to target the CGRP pathway[17]. Ditans, or serotonin (5-HT) 1F receptor agonists, include Lasmiditan that specifically acts on the brain's serotonin receptors.

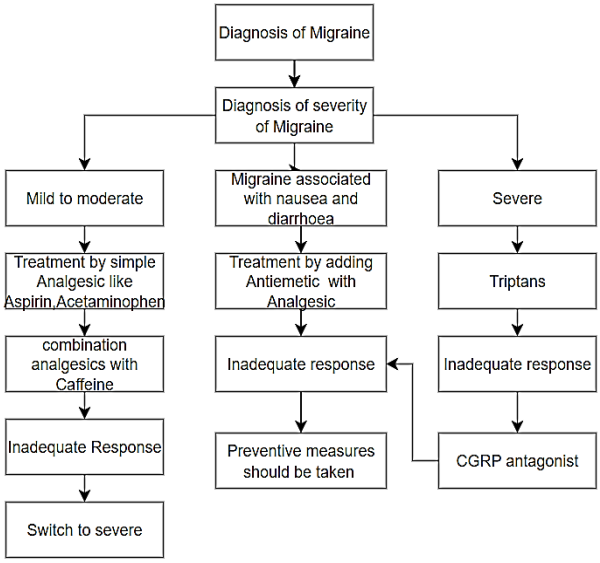

Figure 2. diagnosis of Migraine and its treatment on the basis of severity.

Triptans narrow blood arteries. Lasmiditan is an effective migraine pain reliever without causing vasoconstriction[18]. One neuropeptide that has a role in the pathophysiology of migraines is CGRP. To stop migraine attacks, monoclonal antibodies that target CGRP or its receptor have been created. Among these anti-GRP monoclonal antibodies are galcanezumab, fremanezumab, and erenumab. Usually, they are injected subcutaneously once a month or once every three months. Extended acting, big molecule monoclonal antibodies called CGRP antagonists prevents neuropeptide calcitonin gene-related peptide from working. This neuropeptides are linked with migraine attack pain and vasodilation[19]. Another class of drugs used for migraines

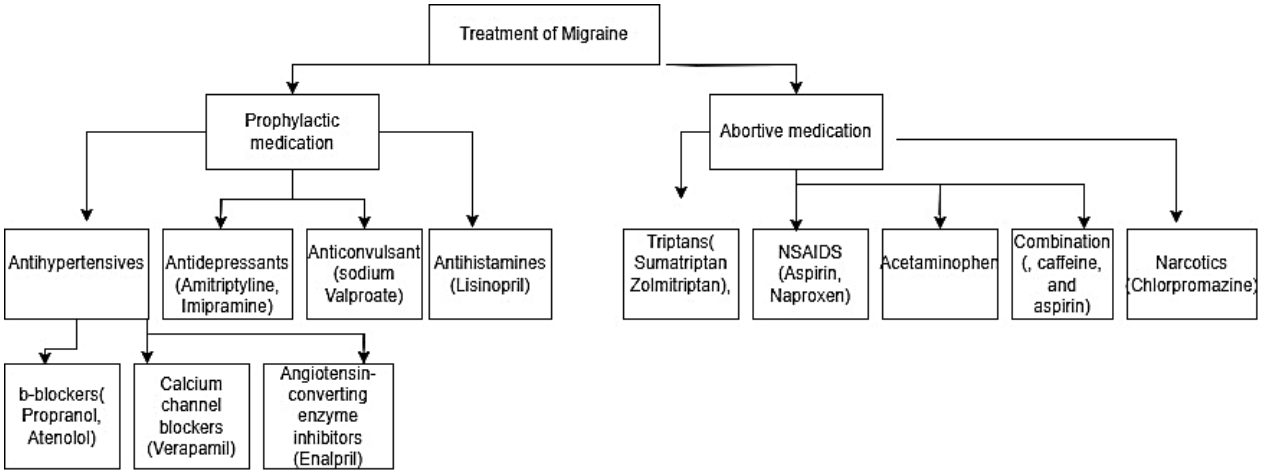

Figure 3 Treatment of migraine headaches

are Gepant CGRP Antagonists. The gepants are small molecule CGRP antagonists that works by blocking the CGRP receptor. For example, Nurtec Oro Dispersible Tablet is a dual therapy used to treat migraines both acutely and preventively. It is taken every other day to prevent episodic migraines and as needed for acute migraine treatment [20]. Qulipta is taken once daily for the preventive treatment of episodic migraine. Combination Therapies in migraine are effective for the treatment and management of migrain. Certain drugs are being created as combination treatments, combining several modes of action to address various aspects of the pathophysiology of migraines. For the acute treatment of migraines, for instance, drugs that combine a triptan with a nonsteroidal anti-inflammatory medicine (NSAID) have been studied.[21] Preventive Antimigraine Medications like β-Blockers (Atenolol Bisoprolol Propranolol), Tricyclics antidepressant (Amitriptyline), Calcium-entry blockers (Flunarizine Verapamil), Anticonvulsants (Divalproex sodium) Anti-inflammatory medications (Aspirin, Naproxen sodium)[22] can be used for treatment of migraine.

Oral Transmucosal Drug Delivery (OTDD)

The introduction of drugs through the oral-mucosa to produce systemic effects is known as oral trans-mucosal drug delivery, or OTDD. It evades the acidic milieu of the stomach and the enzymatic environment of the small intestine, which gives significant advantages over conventional oral medication delivery.[23] When compared to traditional oral delivery, this form of administration often yields a faster systemic delivery since it avoids first-pass metabolism. The first-line treatment for migraines is the use of triptans, which are derivatives of indole. Two dosage forms for zolmitriptan are available i.e. tablets and buccal films. Currently, oral transmucosal administration of Naratriptan (NAR) or its hydrochloride salt (NAR.HCl) is utilized to treat migraine.[24] Drugs can be delivered orally through the mucosal mucosa by buccal, sublingual, or soft palatable routes.

Buccal route

Administration of drugs through buccal route enables the effective and non-invasive delivery of desired therapeutic medicines into the systemic circulation. Because of the high vascularization in the buccal cavity, drugs can enter the systemic circulation directly.[25] By bypassing the first-pass metabolism and getting access to the systemic circulation via the internal jugular vein, the buccal drug delivery system offers low enzymatic degradation, quick onset of action, and excellent bioavailability. The buccal route has the potential to address a gap in migraine treatment. Buccal dosage forms are inexpensive, easy to administer and have better patient adherence. The medication can be easily taken through the buccal-cavity as it is easily accessible and in the event of toxicological effect it can be easily removed and drug absorbtion is stopped.[26] For both local and systemic distribution of medicinal drugs as retentive dose forms, it was discovered that the mucosa of the buccal cavity provided the most convenient and easily reachable region. It is appropriate for medications or excipients that cause minor, reversible mucosal injury or irritation; painless application; easily drug removal; affordable; and better patient compliance.[27] In contrast to ocular, nasal, rectal, and vaginal, it results in higher patient acceptance. Because the oral mucosal layer has a larger surface area than the ocular and nasal mucosal layers, it can also swiftly penetrate mucosal epithelium and absorb low molecular delivery have attracted attention.[28] By keeping the drug dosage form in touch with the absorption site, such as the buccal cavity, and at the site of intended action, mucoadhesion can enhance the localization of drug delivery systems.[29] The most convenient mode of administration for patients includes a rapidly dissolving dosage form that disintegrates and dissolves in saliva and doesn't require water for administration. Patients who may have trouble swallowing conventional tablets, such as those who are bedridden, pediatric, elderly, or developmentally disabled, can benefit from acute treatment when using the suggested drug delivery system.[30] The buccal formulations are an excellent alternative for the oral route since they can carry the medication constantly and controlled. It also tackles the main drawbacks of oral therapy, including hepatic biotransformation, inconsistent drug absorption throughout the gastrointestinal system, and enzymatic degradation.[31] A significant percentage of patients may experience extreme nausea and vomiting during a migraine attack, and oral

therapy may not be effective due to insufficient medication absorption.[32] Improved clinical outcomes, response times, and have been attained with the development of buccal formulations of the acute migraine therapies now on the market.The buccal mucosa recovers cellularly quickly via this pathway. These innovative formulations might assist patients in reaching desired results, such as immediate and quick effect.[33,34]

Table 1. Buccal tablets used in treatment of Migraine

Drug	Dosage form	MOP	Polymers	Key Findings	Reference
Sumatriptan Succinate	Buccal tablet	DC	Hydroxy Propyl Methyl Cellulose HPMC-K4M, Carbopol 934P, ethyl cellulose (EC) and guar gum	Sumatriptan succinate mucoadhesive buccal tablets showed a prolonged therapeutic effect	[44]
Eletriptan hydrobromide	Buccal tablet	DC	chitosan, sodium alginate (SA) and HPMC	For eight hours, sodium alginate and chitosan showed sustained drug release.	[45]
Sumatriptan succinate	bucco-adhesive tablet	DC	HPMC K4M, sodium carboxy methyl cellulose (SCMC), and Carbopol 934P	bucco-adhesive tablet, demonstrated controlled drug release and the results correlated with ex vivo permeation experiments.	[46]
Sumatriptan Succinate	Bilayered buccal tablets	DC	HPMC K4M and HPMC K15M , Carbopol 934P	The combination of Carbopol and HPMC K4M in a 1:1 ratio found in bilayered buccal tablets demonstrated the highest percentage of in vitro drug release within 6 hours.	[47]
Mefenamic acid	mucoadhesive buccal tablet	DC	SA,HPMC-K4M, SCMC	The mucoadhesiveness of the buccal tablet ranges from 0.196 to 0.200. After being put through stability tests in human saliva, there was no change in size or pH. Three hours later, drug release trials indicated 80.7% to 83.4%.	[48]
Naratriptan	Buccal tablet	DC	Carbopol 934 and HPMC K100	Naratriptan was released slowly, completely, and under control over a period of nine hours from matrix tablets	[49]
Sumatriptan Succinate	Mucoadhesive Buccal tablet	DC	Carbopol 934p, Methocel K4M, Methocel K15M and Sodium Carboxy methyl cellulose	Carbopol 934P and Methocel K4m can be utilized to create stable and efficient buccoadhesive tablets containing sumatriptan succinate.	[50]
Prochlorperazine dimaleate	Fast dissolving tablets	DC	crosscarmellose sodium, crospovidone ,sodium starch glycolate, microcrystalline cellulose.	fastest disintegration and successful flavor masking	[51]
eletriptan hydrobromide	Buccal tablets	DC	HMPC, Polyox and sodium alginate	sustained drug release for eight hours.	[52]

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Drug	Dosage form	MOP	Polymers	Key Findings	Reference
zolmitriptan	mucoadhesive buccal tablets.	Wet Granulation	Xanthan gum (Xg), HPMC K4M, carbopol -940, chitosan and SA	Formula F4 containing Xg and HPMC K4M was found to be optimum with 88.8% of drug released at 6 hr	[53]

DC – Direct Compression

Table 2. Buccal Films/Patches used in the treatment of Migraine

Drug	Dosage form	MOP	Excipients	Key Findings	Reference
Rizatriptan	Buccal Film	SCM	HPMC and Eudragit RS 100	When compared to oral solution, pharmacokinetic results showed a noticeably greater rizatriptan plasma level.	[56]
Zolmitriptan	Buccal Bioadhesive Film	SCM	chitosan and polyvinyl alcohol	The mucoadhesion increased if the concentration of *Chitosan* increased and decreased when the concentration of Polyvinyl alcohol was increased.	[57]
Zolmitriptan	Bilayered Mucoadhesive Buccal Patches	SCM	Xanthan gum (XG) HPMC E-15, PVA	XG has the potential to be a mucoadhesive polymer and a drug release modifier in the formulation of zolmitriptan buccal patches.	[58]
Almotriptan	Oral Mucoadhesive Film	SCM	Eudragit RL 100 and Eudragit RS 100,ethyl cellulose,	The films showed rapid hydration and excellent physicomechanical characteristics. A biphasic and significantly higher release of the medication was noted in those with higher hydrophilic polymer concentrations. .	[59]
Almotriptan Malate Eletriptan HBr	Fast Dissolving Oral Films	SCM	HPMC E3LV, HPMC E6LV and HPMC E15LV	Second-generation oral films were found to stable, quickly dissolving for dissolution	[60]
Rizatriptan benzoate	Fast Dissolving Oral Films	Emulsion evaporation method	maltodextrin, gum karaya and xanthan gum, Cinnamonoil polyethylene glycol (PEG) 6000 and starch citric acid	The percentage of drug release from film is 97% in 10 minutes. It shows moderate swelling, , greater therapeutic efficacy may improve the bioavailability..minutes, which is a desirable feature for quick absorption.	[61]
Zolmitriptan	Mucoadhesive Buccal Films	SCM	Citosan,HPMC E5,SCMC	In-vitro drug release studies in the range of 81.93 to 96.85 at the end of 8th hrs	[62]
Rizatriptan	Buccal film	SCM	Proloc, HPMC, and Eudragit RS 100	When compared to an oral solution, pharmacokinetic results showed a noticeably greater rizatriptan plasma level. .	[63]
Zolmitriptan	Bilayered Mucoadhesive Buccal Patches	SCM	Xanthan Gum (XG) HPMC E-15, PVA	XG has the potential to be a mucoadhesive polymer and a drug release modifier in the formulation of zolmitriptan buccal patches.	[64]
Zolmitriptan succinate	Agarose Based	SCM	Agarose, Guar Gum	Based on the formulation's tensile strength, ex vivo mucoadhesion duration, and swelling index, an	[65]

Table 1. Buccal tablets used in treatment of Migraine

Drug	Dosage form	MOP	Polymers	Key Findings	Reference
	Buccal Films			optimal formulation of the buccal film (F15) was chosen.	
Metoclopramide	Mucoadhesive Buccal Patches	SCM	Carboxymethyl Cellulose,Propylene glycol	The mucoadhesive buccal film of Metoclopramide enabled quick drug distribution, avoiding the patient's medication loss from vomiting.	[66]
Zolmitriptan	Buccal Bioadhesive Film	SCM	Chitosan	Buccal film based on chitosan may be utilized for migraine prophylaxis as well as acute treatment.	[67]
Rizatriptan benzoate	Mucoadhesive Buccal Film	SCM	Hydroxypropyl Methylcellulose (HPMC K4M), Polyvinyl Alcohol	The thickness and drug content in the buccal films produced were both consistent. In vitro release for each formulation ranges from 98% to 102% in 40 to 80 minutes.	[68]

SCM - Solvent Casting Method

Table 3 Sublingual formulations used in the treatment of Migraine:-

Drug	Dosage form	MOP	Excipients	Key Findings	Reference
Zolmitriptan	Fast disintegrating sublingual zolmitriptan tablet	Freeze Drying	gelatin mannitol, or amino acid (L-alanin)	When compared to the oral zolmetriptan market product, this sublingual formulation produced a higher and faster plasma concentration of zolmitriptan in rabbits. .	[70]
Zolmitriptan	Fast dissolving sublingual films	SCM	HPMC E50,	Compared to the existing traditional dosage forms, the fast-dissolving sublingual film of Zolmitriptan may be a preferable choice for the acute treatment of migraine attacks.	[71]
Frovatriptan	TPGS stabilized sublingual films	SCM	TPGS (D-α-Tocopherol PEG 1000 succinate), Hydroxyethylcellulose, Gattefose, Polysorbate 80 and Trichloroacetic acid	TPGS was added to the film in order to increase the drug's permeability.	[72]
Frovatriptan	Fast dissolving sublingual films	SCM	Chitosan, HPMC	This study demonstrates the suitability of sublingual films containing frovatriptan as a substitute method of migraine treatment.	[73]
Almotriptan	Sublingual fast dissolving lyophilized tablets	Lyophilization	Polyvinyl pyrrolidone (PVP K25) Chitosan, SA, (PVA), Gelatin Mannitol	A advance and innovative treatment of acute migraine attacks may have been made with the development of sublingual, quickly dissolving Almo-lyotab.	[74]

Table 3 Sublingual formulations used in the treatment of Migraine:-

Drug	Dosage form	MOP	Excipients	Key Findings	Reference
Rizatriptan Benzoate	Sublingual Tablets	Wet Granulation	sodium laurel sulphate and sepitrap 80	When it comes to drugs with low permeability, the combination of sepitrap 80 and polyplasdone XL may hold promise for creating a fast-releasing sublingual tablet with enhanced permeability and bioavailability.	[75]
naproxen sodium granules and naratriptan hydrochloride	Orally disintegrating tablets	Freeze Drying	Sucrose methylcellulose, Sodium alginate, hydroxyethyl starch	Innovative freeze-dried orally disintegrating tablets were effectively created with a unique blend of Naratriptan Hydrochloride and taste-masked Naproxen Sodium.	[76]
Sumatriptan alone and combined with metoclopramide	Fast-dissolving sublingual films	SCM	Hydroxy propyl methyl cellulose	Both the sumatriptan alone and in combination with metoclopramide films demonstrated excellent mucoadhesive qualities and a shorter retention period (15–30 s).	[77]

BUCCAL FORMULATIONS

Glue tablets, films, gels, and fixes are examples of bio-adhesive mucosal structures that arise from a mechanical sequence of processes. The use of polymeric films to deliver prescriptions into buccal holes has tremendous promise in the present era, even with different dosage frames. When it comes to the arrangement of pharmaceutical courses, many alternatives have been continuously introduced for paediatrics, geriatrics, queasy, and rebellious patients.[35]

Buccal bioadhesive tablets

Buccal tablets are a form of medication designed to be placed between the gum and the inner cheek (buccal mucosa) rather than being swallowed or chewed. The medication dissolves slowly and is absorbed through the mucous membranes in the mouth.

Buccal bioadhesive patches

Bioadhesive patches are made up of double layred laminates or multifaceted thin films that are shaped like circles or ovals. They are primarily made of an impervious supporting layer and a bioadhesive polymeric coating that work together to allow drugs to flow through the buccal mucosa unidirectionally.[36] Traditionally, The usual procedure for making patches is to apply drug solution on the surface and let it dry. The size of the patches ranges from 10 to 15 cm2, but they are typically 1 to 3 cm2 in size, possibly ellipsoid in form to fit comfortably in the buccal mucosa's center.

Buccal bioadhesive semisolid

Bioadhesive semisolid buccel dosage forms are composed of either finally powdered natural or synthetic polymers dispersed in a polyethylene or in an aqueous solution. GenerallyDepending on their solubility and concentration, they contain a bioadhesive polymer, medication, and required excipient dissolved or suspended as a fine powder in an aqueous or non-aqueous base.These can be applied with a syringe or on the finger to a target region, and patients find them more agreeable in terms of mouth feel than solid dosage forms; however, they might provide different concentrations of the active components compared to a unit dose form.[37]

Buccal Bioadhesive Powder Dosage Forms

Drug and bioadhesive polymers are combined to create buccal bioadhesive powder dosage forms, which are sprayed into the buccal-mucosa.[38] Though liquids are not easily retained or targeted to the buccal-mucosa, but they have the benefit of being easily disseminated throughout the oral cavity (e.g., as mouthwashes) and would deliver relatively controllable amounts of an active substance. Polymers will adsorb from solution on buccal cells Chitosan yielded the highest binding across the vast range of polymer solutions evaluated, followed by methylcellulose, gelatin, Carbopol 934P, and polycarbophil.[39]

Particulates

Particulates are applied by aerosol, paste, or ointment, but they are most commonly supplied as an aqueous suspension. Particulates have the benefit of being comparatively small, which increases the patient's likelihood of accepting them. However, in contrast to a single-unit dosage form the amount of medication retained on the buccal- mucosa hence, administration is not consistent.[40]

Application of Buccal formulations in Migraine

Buccal Bioadhesive Tablets in Migraine

Drugs can be delivered multidirectionally on the surface or into the buccel cavity using buccal bioadhesive tablets. It is necessary to moisten the dry dosage forms after they come into touch with the buccal mucosa. The bioadhesive raw materials used in the formulation[41-43] will keep a medication in close touch with its absorbent. The systemic therapy

provides some protection against enzymatic degradation, and evade first-pass metabolism. The formulation can be applied directly to a targeted area in local therapy.A bioadhesive polymer (such as polyacrylic acid or cellulose derivative), either alone or in combination, is mixed into a matrix containing the active ingredient and excipients to make a bioadhesive formulation. Table 1 summarizes the role of buccal tablets in the treatment of migraine.

Buccal Bioadhesive Patches and Films

Despite having many of the same benefits and drawbacks as buccal pills, patches tend to be less intrusive and more patient-acceptable due to their thin and flexible design. However, because of their relative thinness, the films are more prone to over-hydration and the loss of their adhesive properties.[54,55] Table 2 shows Buccal Films/Patches used in the treatment of Migraine.

Sublingual formulations used in Migraine

The most promising delivery method for medications that need to be absorbed quickly and have a quick start to effect is sublingual delivery, which increases the drug's bioavailability. This is because the sublingual region has thin mucosa and high vascularity, which allows the medication to enter the bloodstream directly and avoid the first pass effect. By evading the hepatic first-pass metabolism and reducing the gastrointestinal (GI) dysmotility which is typically related to the migraine attacks, sublingual route of delivery gives combined benefits of convenience, patient compliance, the ability to administer the drugnin the absence of water, and quick disintegration, dissolution, and pre-gastric absorption in the sublingual area[69] Table 3 shows Sublingual formulations used in the treatment of Migraine.

Soft palatal drug delivery

Because the novelistic trans-soft palate route lacks nonkeratinized, less salivary production, which results in minimal drug loss into the saliva, it has a clever inherent advantage over other transmucosal routes like the buccal, sublingual, gastric, colon mucosa, etc..[78] Because the soft palate tissue lacks proteolytic enzymes, medication degradation and dosage decrease are prevented. Compared to other mucosa, the soft palate has a lower rate of cellular turnover.[79] The innovative oral soft palatal platform presents a viable mucoadhesive site for local and systemic delivery of active pharmaceuticals, and it can also used as a pathway for drug delivery to the brain. Because palatal region is flexible, it is simple to access mobile tissue and place the dose form there. To ensure a regulated medication release, the dosage form with mucoadhesive qualities will stay at the site for a considerable amount of time after it is placed there.[80] However palatable route has not been explored in the treatment of migraine. It is therefore recommended that dosage form must be deign to give drug delivery by this route.

CONCLUSION

For the treatment of migraine oral transmucosal formulations have been used successfully with better patient compliance and with increased bioavailability. Oral transmucosal formulations like buccal patches, buccal films, mouth-dissolving strips, soft palatable formulations, sublingual tablets and films have been used to produce systemic effects by bypassing first-pass metabolism in a non-invasive manner. It also overcomes the main drawbacks of oral therapy, including hepatic biotransformation, varying drug absorption across the gastrointestinal system, and enzymatic degradation. These formulations produce immediate effects as well as controlled release effects in the treatment of migraine. However gingival, palatal, and labial mucosal delivery has not been explored for the treatment of migraine. Therefore more comprehensive researches are needed to explore OTDD for the treatment of migraine and another neurodegenerative disease.

Acknowledgments

Authors conveyed special thanks to Mr. Jitender Joshi, Chancellor, and Prof. (Dr.) Dharam Buddhi, Vice Chancellor of Uttaranchal University-Dehradun encourages publishing this research work.

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